Supporting Information for:

Multiple Strategies to Produce Lipophilic Nanoparticles leaving watersoluble poly(HPMA)

*Raffaele Ferrari*¹, Marco Callari² and Davide Moscatelli^{2,*}

¹Institute for Chemical and Bioengineering, Department of Chemistry and Applied Biosciences, ETH Zurich, Vladimir-Prelog-Weg 1, 8093, Zurich, Switzerland. ²Department of Chemistry, Materials and Chemical Engineering, Politecnico di Milano, Via Mancinelli 7 - 20131 Milano, Italy.

*: Corresponding author: Davide Moscatelli; E-mail: <u>davide.moscatelli@polimi.it</u> Phone: +39 02 2399 3135

1. HPMA Synthesis

To produce the monomer Na_2CO_3 (12.61 g, 119 mmol) was suspended in DCM (28 mL). The mixture was cooled to -10 °C and amino-2-propanol (8.35 mL, 108 mmol) was added. Distilled methacryloyl chloride (10.56 mL, 108 mmol) in 11 mL of DCM was added at flow rate of 1 mL/min with the solution kept at -10 °C (acetone/dry ice mixture) and vigorously stirred. The mixture was stirred for 20 min at 5 °C and then left stirring to equilibrate to room temperature. Following filtration, the filtrate was dried twice with anhydrous Na_2SO_4 and concentrated until formation of crystallization seeds. The product was left to crystallize at -20 °C overnight, washed with cold DCM and recrystallized from acetone (68% yield). NMR spectrum proving the HPMA purity is reported in **Figure S1**.



Figure S1. ¹H-NMR of the HPMA.

2. Macromonomer Characterization



Figure S2. NMR spectrum of HPMA-LA₈ together with the integrated peaks.

3. NPs via Flash Nanoprecipitation

Figure S3 reports PDI data of the NPs reported in Figure 3a in the main manuscript.



Figure S3. Polydispersity Index versus polymer concentration in the starting organic phase for: (a) HPMA-based copolymer and (b) HPMA-based copolymer co-dissolved with high MW PLA. The adopted copolymers are: poly(HPMA-LA₄-co-PEGMA₁₉) (\blacksquare), poly(HPMA-LA₆-co-PEGMA₁₉) (\blacklozenge), poly(HPMA-LA₈-co-PEGMA₁₉) (\blacklozenge), poly(HPMA-LA₈-co-PEGMA₄₅) (\square) and poly(HPMA-LA₈-co-PEGMA₄₅) (\square).

4. Copolymer characterization

The NMR of poly(HPMA-LA₈-co-PEGMA₄₅) obtained after the synthesis is reported below.



Figure S4. H-NMR spectrum oft he poly(HPMA-LA₈-co-PEGMA₄₅) copolymer

It is possible to observe that no peaks are present in the region between 5.4 and 6.2 ppm meaning that the full macromonomer conversion is achieved (no vinyl signals are present). In addition, the copolymer composition and the expected peak ratio have been observed confirming the average composition of the copolymer. Such theoretical values have been evaluated as follows:

hydrogen per repeating LA unit (A: 5 – 5.2 ppm):	1
LA units per pendant chain (related to signal A) :	7
LA fraction in the copolymer:	0.8
hydrogen per repeating PEG unit (B: 3.63 ppm):	4
PEG units per pendant chain (related to signal B):	44
PEG fraction in the copolymer:	0.2

The expected signal then becomes:

1*7*0.8 = 5.6
4*44*0.2 = 35.2
0.137
0.863
0.13
0.87

Finally, it is worth noticing that such analyses were repeated and confirmed for the different copolymers produced.